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the BALKAN-AF survey

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ORIGINAL ARTICLE

Adherence to the ABC (Atrial fibrillation Better Care) pathway in the Balkan region: the BALKAN-AF survey

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KEY WORDS

atrial fibrillation, BALKAN-AF survey, oral anticoagulants, rate control, rhythm control

EDITORIAL

by Pignatelli, Violi, Pastori, see p. 176

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ABSTRACT

INTRODUCTION The Atrial fibrillation Better Care (ABC) pathway provides a useful way of simplifying decision-making considerations in a holistic approach to atrial fibrillation management.

OBJECTIVES To evaluate adherence to the ABC pathway and to determine major gaps in adherence in patients in the BALKAN-AF survey.

PATIENTS AND METHODS In this ancillary analysis, patients from the BALKAN-AF survey were divided into the following groups: A (avoid stroke) + B (better symptom control) + C (cardiovascular and comorbidity risk management)-adherent and -nonadherent management.

RESULTS Among 2712 enrolled patients, 1013 (43.8%) patients with mean (SD) age of 68.8 (10.2) years and mean CHA_2DS_2-VASc score of 3.4 (1.8) had A+B+C-adherent management and 1299 (56.2%) had A+B+C-nonadherent management. Independent predictors of increased A+B+C-adherent management were: capital city (odds ratio [OR], 1.23; 95% CI, 1.03–1.46; $P = 0.02$), treatment by cardiologist (OR, 1.34; 95% CI, 1.08–1.66; $P = 0.01$), hypertension (OR, 2.2; 95% CI, 1.74–2.77; $P < 0.001$), diabetes mellitus (OR, 1.28; 95% CI, 1.05–1.57; $P = 0.01$), and multimorbidity (the presence of 2 or more long-term conditions) (OR, 1.85; 95% CI, 1.43–2.38; $P < 0.001$). Independent predictors of decreased A+B+C-adherent management were: age 80 years or older (OR, 0.61; 95% CI, 0.48–0.76; $P < 0.001$) and history of bleeding (OR, 0.5; 95% CI, 0.33–0.75; $P = 0.001$).

CONCLUSIONS Physicians' adherence to integrated AF management based on the ABC pathway was suboptimal. Addressing the identified clinical and system-related factors associated with A+B+C-nonadherent management using targeted approaches is needed to optimize treatment of patients with AF in the Balkan region.

INTRODUCTION The Atrial fibrillation Better Care (ABC) pathway for holistic management, introduced in 2017, provides a useful approach (A, avoid stroke with anticoagulation; B, better symptom management with rate or rhythm control; C, cardiovascular and comorbidity risk management)

WHAT'S NEW?

Countries in the Balkan region were largely underrepresented in recent registries on atrial fibrillation. Our study evaluated adherence to the Atrial fibrillation Better Care (ABC) holistic approach and determine major gaps in adherence to the ABC pathway among participants of the BALKAN-AF survey. Physicians' adherence to integrated atrial fibrillation management based on the ABC pathway was suboptimal in our study. Multivariable predictors of A+B+C-nonadherent management were age 80 years or older and a history of bleeding, whilst capital city, treatment by cardiologist, hypertension, diabetes mellitus, and multimorbidity were independently associated with A+B+C-adherent management.

that simplifies decision-making considerations, especially in busy clinics and ward settings.[1] The A component of the ABC pathway includes identifying patients with low risk of stroke based on the CHA_2DS_2-VASc (congestive heart failure [HF], hypertension, age 75 years or older, diabetes, stroke / transient ischemic attack, vascular disease, age 65 to 74 years, sex category) score. Individuals with 1 or more risk factors for stroke should be offered stroke prevention (either a vitamin K antagonist with a well-managed time in therapeutic range or a non–vitamin K antagonist oral anticoagulant). The B component focuses on optimizing symptoms of atrial fibrillation with rate or rhythm control. The C component is to address comorbidities or concomitant risk factors, like hypertension, HF, diabetes mellitus, cardiac ischaemia, and sleep apnea, including lifestyle changes (such as lowering excessive body weight, regular physical activity, and reducing alcohol and stimulant use). Patients' values and preferences should be considered.[1] The idea of integrated care has been popularized to improve patient outcomes.[2] Compliance with the ABC pathway has been associated with a decreased rate of cardiovascular events[3,4] and significantly lower healthcare costs[5] compared with noncompliance with the ABC approach.

Given the evident benefits of the ABC pathway, there is a need for systematic collection of real-world data concerning adherence to integrated management of patients with atrial fibrillation (AF), since registry-based data may enable the identification of barriers for evidence-based treatment of AF patients in clinical practice. Contemporary registries provide useful insights into prevailing clinical patterns of AF management among physicians across Europe. However, countries in the Balkan region were largely under-represented in recent registries and data regarding management of patients with AF in most of these countries are scarce.

The aim of this study was to investigate adherence to the ABC holistic approach and determine major gaps in adherence to the ABC pathway among participants of the BALKAN-AF survey.

PATIENTS AND METHODS An outline of the BALKAN-AF survey has been previously published.[6] This survey was created to prospectively collect real-world data concerning consecutive patients with nonvalvular AF documented on electrocardiography. Patients managed in hospitals and outpatient settings were included, irrespective of whether AF was the main reason for the visit or stay in the hospital. Patients were assessed by a cardiologist or an internal medicine specialist if a cardiologist was not available. Participating countries were: Albania, Bosnia and Herzegovina, Bulgaria, Croatia, Montenegro, Romania, and Serbia (a total of more than 50 million inhabitants). Each country recruited university and nonuniversity hospitals and outpatient health centers located in different cities or rural areas.

This 14-week (performed from December 2014 to February 2015), multicenter (a total of 49 centers), observational survey was created and conducted by the Serbian Atrial Fibrillation Association. The snapshot registry was introduced to the national cardiology societies or relevant working groups in certain Balkan countries. The respective national coordinator selected the centers which precisely reflected AF management in a particular country in daily clinical practice. In participating countries, the registry was approved by the national and / or local institutional review board. An informed consent form was collected from the patients before enrolment. The study protocol is consistent with the ethical guidelines of the 1975 Declaration of Helsinki.

Patients with prosthetic mechanical heart valves, moderate or severe mitral valve stenosis, or any significant heart valve disease with indications for surgical treatment and those younger than 18 years were not included in the study.

Data were collected using an electronic case report form, and the following information was acquired: patients' clinical characteristics and AF-related characteristics, healthcare facility type and location, patients' physical findings and management at the enrollment visit and further management after discharge. All cardiovascular risk factors, diseases, and risk scores were defined according to individual European Society of Cardiology guidelines, other guidelines, scientific statements and textbooks presented previously in supplementary information.[7] Stroke risk was evaluated using the CHA_2DS_2--VASc score.[8] Bleeding risk was evaluated using the HAS-BLED (hypertension, abnormal renal / liver function, stroke, bleeding history or predisposition, labile international normalized ratio [INR], elderly [>65 years], drugs or alcohol concomitantly) score.[8]

There was no regular monitoring of centers and follow-up visits. Consecutiveness of enrolled patients, correctness and completeness of data were confirmed by the national coordinators and all investigators.

In this ancillary analysis, patients were divided into A+B+C-adherent and A+B+C-nonadherent management groups.

A-adherent management was defined as the use of oral anticoagulants (OAC) in patients with AF with a CHA_2DS_2-VASc score of 1 or more (men) or 2 or more (women), or no OAC in those with a CHA_2DS_2-VASc score of 0 (men) or 1 (women).

A-nonadherent management was defined as concomitant use of antiplatelet therapy without clinical indications, or no OAC use in patients with indications for OAC therapy.

B-adherent management was classified as rate or rhythm control strategy in patients with European Heart Rhythm Association (EHRA) symptom score of 2 or more. Patients with EHRA symptom score less than 2 were not included in the B-adherent management group.

B-nonadherent management was neither rate nor rhythm control in patients with EHRA symptom score of 2 or higher. Patients with EHRA symptom score of less than 2 were not included in the B-nonadherent management group.

C-adherent management was defined as the use of concomitant disease-specific treatment(s) according to current guidelines or no management in case of no comorbidities.[9-12]

C-nonadherent management was defined as the lack of use of concomitant disease-specific treatment according to current guidelines.

Statistical analysis Categorical variables were expressed as absolute frequencies and percentages, and continuous variables as mean (SD). Categorical variables with normal distribution were compared with the *t* test. Continuous variables with skewed distribution were compared with the Mann–Whitney test. The descriptive analysis involved baseline characteristics of A+B+C-adherent and -nonadherent patients. Comparative analyses among patients with A, B, C, A+B, or A+B+C-adherent management were performed using univariate and multivariate logistic regression analyses. Statistically significant variables on univariate logistic regression model were entered into multivariate logistic regression model to identify multivariable predictors of A, B, C, A+B, and A+B+C-adherent management. Results are showed as odds ratio (OR) with 95% CI. A 2-sided *P* value of less than 0.05 was interpreted as significant. All analyses were performed using the SAS software, version 9.4 (SAS Institute Inc., Cary, North Carolina, United States).

RESULTS

Patient characteristics In this analysis, 2712 patients were enrolled at 49 centers in 7 countries. Complete data on A+B+C-adherent or -nonadherent management were available in 2312 patients (85.3%). Patients in the ABC-adherent management group were more likely to be women ($P = 0.02$) and more frequently had hypertension ($P < 0.001$), diabetes mellitus (DM) ($P = 0.01$), history of percutaneous coronary intervention / stenting ($P = 0.01$), thyroid disease ($P = 0.04$), and multimorbidity (defined as the presence of 2 or more long-term conditions)[13] ($P = 0.001$). They were less likely to have paroxysmal AF ($P = 0.04$), asymptomatic AF ($P < 0.001$), HF ($P < 0.001$), history of myocardial infarction ($P = 0.004$), anemia ($P < 0.001$), or prior bleeding events ($P = 0.03$). Patient characteristics are shown in TABLE 1.

Stroke and bleeding risk profile The mean CHA_2DS_2-VASc ($P = 0.41$) and HAS-BLED score ($P = 0.31$) values were similar in both groups (TABLE 2). Patients with A+B+C-adherent management had lower prevalence of a CHA_2DS_2-VASc score of 0 ($P < 0.001$) and a CHA_2DS_2-VASc score of 0 in men or 1 in women ($P < 0.001$), and were more likely to have a CHA_2DS_2-VASc score of 2 or higher ($P = 0.01$) (TABLE 2).

Stroke prevention strategies Patients in the A+B+C-adherent management group were more likely to receive OAC overall ($P < 0.001$), OAC alone ($P < 0.001$), NOAC ($P < 0.001$), VKA ($P < 0.001$), dual antithrombotic therapy ($P < 0.001$), or triple antithrombotic therapy ($P < 0.001$), and less likely to have single antiplatelet therapy (SAPT) alone ($P < 0.001$), dual antiplatelet therapy (DAPT) alone ($P < 0.001$), or no antithrombotic therapy ($P < 0.001$) (TABLE 2).

Patients with A+B+C-adherent management were more likely to receive acenocoumarol ($P < 0.001$), warfarin ($P < 0.001$), dabigatran ($P < 0.001$), rivaroxaban ($P < 0.001$), and apixaban ($P < 0.001$) (TABLE 2). Only one patient had a history of percutaneous left atrial appendage closure.

Adherence to recommendations on stroke prevention from the ABC pathway Data on A-adherent management were available for 2671 patients (98.5%). Among patients with a CHA_2DS_2-VASc score of 0 (men) or 1 (women), 70 (53.0%) received OAC alone, 12 (9.2%) used SAPT alone, 1 (0.7%) used DAPT alone, 5 (3.8%) used dual antithrombotic therapy, and 44 (33.3%) received no antithrombotic therapy (Supplementary material, *Table S1*).

Among patients with high stroke risk (CHA_2DS_2-VASc score ≥2), 1048 (59.9%) received OAC alone, 214 (12.2%) used SAPT alone, 88 (5.0%) used DAPT alone, 190 (10.9%) received dual antithrombotic therapy, 68 (3.5%) used triple antithrombotic therapy, and 143 (8.5%) had no antithrombotic therapy (Supplementary material, *Figure S1*).

HAS-BLED score strata are presented in the Supplementary material, *Figure S2*. Among patients with HAS-BLED score of less than 3, 98 (7.4%) received dual antithrombotic therapy, whilst of those with HAS-BLED score of 3 or higher, 80 (12.7%) were treated with dual antithrombotic therapy.

The mean (SD) most recent INR was 2.42 (1) in patients on VKA, and in 522 patients (55.2%) the INR value was within therapeutic range (from 2 to 3).

Adherence to the ABC recommendations on better symptom management Among 2106 symptomatic patients (defined as having an EHRA symptom

TABLE 1 Patient clinical characteristics according to adherence to the Atrial fibrillation Better Care pathway

Variable		ABC-nonadherent (n = 1299)	ABC-adherent (n = 1013)	*P* value
Age, y	Mean (SD)	69.7 (11.6)	68.8 (10.2)	0.06
	Range	21–96	18–95	–
Female sex		557 (42.9)	485 (47.9)	0.02
Alcohol abuse		58 (4.5)	47 (4.6)	0.84
Paroxysmal AF		494 (38)	344 (34)	0.04
Persistent AF		157 (12.1)	151 (14.9)	0.14
Permanent AF		550 (42.3)	392 (38.7)	0.08
AF history <1 year		180 (13.9)	144 (14.2)	0.97
AF history >5 years		255 (19.6)	205 (20.2)	0.99
Asymptomatic AF currently		206 (15.9)	0 (0)	<0.001
Symptomatic AF currently[a]		1093 (84.1)	1013 (100)	<0.001
EHRA symptom score, %, mean (SD)		2.2 (0.8)	2.5 (0.6)	<0.001
Heart rate, bpm, mean (SD)		92.3 (29.3)	94.0 (28.9)	0.17
Systolic BP, mm Hg, mean (SD)		132.2 (23)	136.8 (21.4)	<0.001
Diastolic BP, mm Hg, mean (SD)		79.6 (12.3)	82.1 (12.4)	<0.001
First diagnosed AF		348 (26.8)	251 (24.8)	0.27
Lone AF		36 (2.8)	17 (1.7)	0.08
Concomitant diseases				
Prior or current HF		684 (52.7)	413 (40.8)	<0.001
DCM		113 (8.7)	84 (8.3)	0.73
Symptoms of HF currently		657 (50.6)	415 (41)	<0.001
Hypertension		882 (67.9)	898 (88.6)	<0.001
CAD		435 (33.5)	306 (30.2)	0.09
Prior MI		220 (17)	122 (12)	0.004
History of PCI/stenting		100 (7.7)	95 (9.4)	0.01
Mitral valve regurgitation		456 (35.1)	315 (31.1)	0.04
Aortic valve disease		173 (13.3)	112 (11.1)	0.10
PAD		56 (4.3)	47 (4.6)	0.71
Thyroid disease		120 (9.2)	121 (11.9)	0.04
Diabetes mellitus		302 (23.2)	287 (28.3)	0.01
Anemia		238 (18.3)	113 (11.1)	<0.001
CKD		227 (17.5)	153 (15.1)	0.13
COPD		197 (15.2)	125 (12.3)	0.049
Sleep apnea		21 (1.6)	28 (2.8)	0.06
Dementia		45 (3.5)	21 (2.1)	0.045
Malignancy		57 (4.4)	46 (4.5)	0.88
Liver disease		61 (4.7)	29 (2.9)	0.02
Prior stroke		142 (10.9)	100 (9.9)	0.40
Prior TIA		35 (2.7)	38 (3.8)	0.15
Prior SE		10 (0.8)	8 (0.8)	0.96
Prior bleeding		72 (5.5)	37 (3.7)	0.03
Obesity		328 (25.3)	250 (24.7)	0.83
Multimorbidity[b]		1063 (81.8)	921 (90.9)	<0.001

Data are presented as number (percentage) of patients unless otherwise indicated.

a EHRA symptom score ≥2

b The presence of 2 or more long-term conditions[13]

Abbreviations: ABC, Atrial fibrillation Better Care; AF, atrial fibrillation; BP, blood pressure; CAD, coronary artery disease; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; DCM, dilated cardiomyopathy; EHRA, European Heart Rhythm Association; HF, heart failure; MI, myocardial infarction; PAD, peripheral artery disease; PCI, percutaneous coronary intervention; SE, systemic embolism; TIA, transient ischemic attack

TABLE 2 Stroke and bleeding risk as well as stroke prevention strategies in patients according to adherence to the Atrial fibrillation Better Care pathway

Variable	ABC-nonadherent (n = 1299)	ABC-adherent (n = 1013)	*P* value
CHA_2DS_2-VASc score, mean (SD)	3.4 (1.9)	3.4 (1.8)	0.41
CHA_2DS_2-VASc score 0	67 (5.1)	15 (1.5)	<0.001
CHA_2DS_2-VASc score 0 (men) or 1 (women)	100 (7.7)	21 (2.1)	<0.001
CHA_2DS_2-VASc score ≥2	1096 (84.4)	893 (88.2)	0.01
HAS-BLED score, mean (SD)	1.94 (1.2)	1.99 (1.2)	0.31
HAS-BLED score <3	906 (69.7)	698 (68.9)	0.79
HAS-BLED score ≥3	393 (30.3)	315 (31.1)	0.66
Stroke prevention			
Overall OAC	594 (45.7)	992 (97.9)	<0.001
OAC alone	506 (39)	836 (82.5)	<0.001
NOAC	81 (6.2)	191 (18.9)	<0.001
Rivaroxaban	25 (1.9)	71 (7)	<0.001
Dabigatran	45 (3.5)	90 (8.9)	<0.001
Apixaban	11 (0.8)	30 (3)	<0.001
VKA	513 (39.5)	821 (81)	<0.001
Acenocoumarol	353 (27.1)	541 (53.4)	<0.001
Warfarin	160 (12.3)	279 (27.5)	<0.001
Single antiplatelet therapy alone	318 (24.5)	0	<0.001
DAPT alone	120 (9.2)	0	<0.001
Dual antithrombotic therapy	69 (5.3)	127 (12.5)	<0.001
Triple antithrombotic therapy	19 (1.5)	49 (4.8)	<0.001
No antithrombotic therapy	264 (20.3)	21 (2.1)	<0.001

Data are presented as number (percentage) of patients unless otherwise indicated.

Abbreviations: CHA_2DS_2-VASc, congestive heart failure, hypertension, age ≥75 years, diabetes, stroke/transient ischemic attack, vascular disease, age 65 to 74 years, sex category; DAPT, dual antiplatelet therapy; HAS-BLED, hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile international normalised ratio, elderly (>65 years), drugs or alcohol concomitantly; NOAC, non–vitamin K antagonist oral anticoagulants; OAC, oral anticoagulants; VKA, vitamin K antagonists; others, see TABLE 1

score of ≥2), 689 (32.7%) were managed using a rhythm control strategy and 1311 (62.3%) underwent a rate-control strategy. Overall, 514 (24.4%) patients were prescribed amiodarone, 174 (8.3%) received propafenone, 1544 (73.3%) used a β-blocker, 91 (4.3%) used verapamil, 563 (26.7%) used digoxin, and 62 (2.9%) were scheduled for electrical cardioversion. Other medications and strategies are listed in TABLE 3.

Adherence to cardiovascular and comorbidity risk management from the ABC pathway The prevalence and management of the most frequent comorbidities are specified in TABLE 4. β-Blockers were the most prevalent agents in the management of coronary artery disease (CAD), HF, and hypertension. Angiotensin-converting enzyme inhibitors were the second most frequently used drugs for patients with CAD and hypertension, and loop diuretics were used in 72.3% of patients with HF (TABLE 4).

A-adherent management Among 2671 patients (98.5%) with available data on the stroke prevention strategy, 1991 patients (74.5%) were managed by an A-adherent strategy, whilst 680 patients (25.5%) had an A-nonadherent management.

Independent predictors of A-adherent management were: capital city (OR, 2.27; 95% CI, 1.87–2.76; *P* <0.001), treatment by cardiologist (OR, 1.34; 95% CI, 1.08–1.67; *P* = 0.01), hypertension (OR, 1.73; 95% CI, 1.40–2.15; *P* <0.001), dilated cardiomyopathy (OR, 1.90; 95% CI, 1.27–2.85; *P* = 0.002), and thyroid disease (OR, 1.49; 95% CI, 1.07–2.06; *P* = 0.002) (Supplementary material, *Table S1*), whereas age 80 years or older (OR, 0.49; 95% CI, 0.41–0.63; *P* <0.001), paroxysmal AF (OR, 0.47; 95% CI, 0.39–0.57; *P* <0.001), and CAD (OR, 0.76; 95% CI, 0.63–0.92; *P* = 0.01) were independently associated with a lower likelihood of A-adherent management (Supplementary material, *Table S1*).

B-adherent management Among 2106 symptomatic patients (an EHRA symptom score of ≥2), 1899 (90.2%) received B-adherent management, whereas 207 (9.8%) received B-nonadherent treatment.

Independent predictors of lower likelihood of B-adherent management were: paroxysmal AF (OR, 0.68; 95% CI, 0.5–0.9; *P* = 0.01) and AF history of less than 1 year (OR, 0.64; 95% CI, 0.42–0.98; *P* = 0.04) (Supplementary material, *Table S1*).

C-adherent management Among 2702 patients (99.6%) with available data on C-adherent management, 1951 patients (72.2%) received C-adherent management, whilst 751 patients (27.8%) had C-nonadherent management. Independent predictors of C-adherent management were: capital city (OR, 1.37; 95% CI, 1.14–1.64; *P* = 0.001), nonemergency center (OR, 2.14; 95% CI, 1.74–2.63; *P* <0.001), paroxysmal AF (OR, 1.35; 95% CI, 1.08–1.70; *P* = 0.01), first-diagnosed AF (OR, 1.51; 95% CI, 1.22–1.88; *P* <0.001), hypertension (OR, 8.96; 95% CI, 7.05–11.38; *P* <0.001), DM (OR, 1.86; 95% CI, 1.49–2.31, *P* <0.001), and prior TIA (OR, 2.18; 95% CI, 1.17–4.08; *P* = 0.01), whilst age 80 years or older (OR, 0.69; 95% CI, 0.55–0.86; *P* = 0.002), HF (OR, 0.15; 95% CI, 0.12–0.19; *P* <0.001), chronic kidney disease (OR, 0.55; 95% CI, 0.44–0.69; *P* <0.001), and history of bleeding (OR, 0.56; 95% CI, 0.38–0.81; *P* = 0.002) were negatively associated with C-adherent management on multivariable analysis (Supplementary material, *Table S1*).

A+B+C-adherent management Data on A+B+C-adherent management were available in 2312 patients (85.3%). Among these, 1013 patients (43.8%) had A+B+C-adherent management and 1299 (56.2%) had A+B+C-nonadherent management.

Independent predictors of the A+B+C-adherent management were: capital city (OR, 1.23; 95% CI, 1.03–1.46; *P* = 0.02), treatment by cardiologist (OR, 1.34; 95% CI, 1.08–1.66; *P* = 0.07), hypertension (OR, 2.20; 95% CI, 1.74–2.77; *P* <0.001),

TABLE 3 Management of symptomatic patients from the BALKAN-AF survey

Variable	Symptomatic patients[a] (n = 2106)
Rhythm control	689 (32.7)
Rate control	1311 (62.3)
Current β-blocker	1544 (73.3)
Current verapamil	91 (4.3)
Current diltiazem	18 (0.9)
Current digoxin	563 (26.7)
Current propafenone	174 (8.3)
Current flecainide	1 (0.1)
Current sotalol	17 (0.8)
Current dronedarone	2 (0.1)
Current amiodarone	514 (24.4)
ECV currently or in the future	62 (2.9)
AF catheter ablation currently or in the future	47 (2.2)
AF surgery currently or in the future	1 (0.1)
Atrioventricular node ablation currently or in the future	5 (0.2)

Data are presented as number (percentage) of patients.

a EHRA II-IV

Abbreviations: ECV, electrical cardioversion; others, see TABLE 1

TABLE 4 Management of the most prevalent comorbidities in the BALKAN-AF survey

Variable	Hypertension (n = 2121)	HF (n = 1163)	CAD (n = 821)	Diabetes mellitus (n = 668)
ACEI	1159 (54.6)	508 (43.7)	406 (49.4)	NA
AT1 receptor antagonist	467 (22)	262 (22.5)	176 (21.4)	NA
Calcium channel blocker	525 (24.7)	NA	19 (2.3)	NA
β-Blocker	1592 (75)	882 (75.8)	629 (76.6)	NA
Thiazide diuretic	562 (26.5)	222 (19.1)	NA	NA
Spironolactone	NA	316 (27.2)	NA	NA
Eplerenone	NA	NA	NA	NA
Loop diuretic	NA	839 (72.3)	NA	NA
Aspirin	NA	NA	374 (45.5)	NA
Statin	NA	NA	522 (63.6)	NA
Other lipid lowering agent	NA	NA	10 (1.2)	NA
Lifestyle modifications	NA	NA	NA	145 (21.7)
Insulin therapy	NA	NA	NA	153 (22.9)
Oral antidiabetic drugs	NA	NA	NA	442 (66.2)

Data are presented as number (percentage) of patients.

Abbreviations: ACEI, angiotensin-converting-enzyme inhibitor; AT1, angiotensin-type-1; NA, not available; others, see TABLE 1

DM (OR, 1.28; 95% CI, 1.05–1.57; $P = 0.01$), and multimorbidity (OR, 1.85; 95% CI, 1.43–2.38; $P < 0.001$). Age of 80 years or older (OR, 0.61; 95% CI, 0.48–0.76; $P < 0.001$) and history of bleeding (OR, 0.50; 95% CI, 0.33–0.75; $P = 0.001$) were associated with lower likelihood of A+B+C-adherent management.

AF history of less than 1 year (OR, 0.65; 95% CI, 0.40–1.07; $P = 0.09$) and AF history of over 5 years (OR, 0.69; 95% CI, 0.43–1.11; $P = 0.13$) were not associated with the A+B+C-adherent management.

DISCUSSION The main finding of this ancillary analysis is that in the participating Balkan countries, physicians' adherence to the ABC pathway for holistic management of patients with AF was suboptimal, with less than half of patients with AF receiving A+B+C-adherent management.

Multivariable predictors of A+B+C-nonadherent management were age of 80 years or older and history of bleeding, whilst capital city, treatment by cardiologist, hypertension, DM, and multimorbidity were independently associated with A+B+C-adherent management. The ABC pathway simplifies treatment decision-making in a holistic approach to AF management, thus allowing a streamlined approach to AF care that can bridge primary and secondary care, cardiologist and non-cardiologist and improve patient understanding ("as easy as ABC").

Our study highlighted the unmet needs and knowledge gaps that should be addressed to improve the care for patients with AF in the Balkan countries. Patients aged 75 years or older have an increased risk for stroke and major bleeding, but the effects of OACs are consistent in older age strata in comparison with younger patients.[14] The BAFTA (Birmingham Atrial Fibrillation Treatment of the Aged) study,[15] a randomized controlled trial WASPO (Warfarin Versus Aspirin for Stroke Prevention in Octogenarians with AF),[16] and a large nationwide cohort study from Taiwan[17] support the use of VKAs or NOACs in patients with AF aged 75 years or older. Available data also support the use of rhythm or rate-control strategy and implementation of integrated AF management in elderly patients to improve quality of life and to relieve symptoms.[8]

Bleeding history should not be an excuse to withhold OAC therapy. Regular reassessment of bleeding risk should be a part of management compliant with the ABC pathway.[18] Patients with high risk of bleeding should receive OAC with close monitoring and frequent follow-up visits.[8] The net clinical benefit of OAC in these patients is evident.[19]

In our study, multimorbidity was an independent predictor of better A+B- and A+B+C-adherent management. In one study,[20] both over- and underuse of OAC were present in patients with multimorbidity and indications to OAC. Some studies have revealed that multimorbidity is significantly more prevalent in patients with AF than in those without AF.[21] Multimorbidity is also associated with worse survival of patients with AF,[21,22] and AF patients with multimorbidity have higher stroke and bleeding risk. The abovementioned findings should be related to prioritizing patients with AF and multimorbidity for optimal management according to the ABC pathway.

TABLE 5 Independent predictors of A+B+C-adherent management in the Balkan region (see also Supplementary material, *Table S1*)

Variable	Univariate analysis		Multivariate analysis	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Age ≥80 years	0.61 (0.46–0.74)	<0.001	0.61 (0.48–0.76)	<0.001
Capital city	1.17 (1.01–1.41)	<0.001	1.23 (1.03–1.46)	0.02
University center	1.46 (1.13–1.89)	0.003	1.37 (0.81–1.69)	0.425
Treatment by cardiologist	1.31 (1.05–1.59)	0.01	1.34 (1.08–1.66)	0.01
Nonemergency center	1.31 (1.07–1.60)	0.01	1.39 (0.93–1.69)	0.658
Hypertension	2.16 (1.71–2.72)	<0.001	2.2 (1.74–2.77)	<0.001
Diabetes mellitus	1.23 (1.00–1.50)	0.04	1.28 (1.05–1.57)	0.01
Bleeding events	0.52 (0.34–0.79)	0.002	0.5 (0.33–0.75)	0.001
Thyroid disease	1.34 (1.02–1.75)	0.03	1.42 (0.88–1.83)	0.14
Multimorbidity[a]	1.47 (1.13–1.92)	0.004	1.85 (1.43–2.38)	<0.001

a The presence of 2 or more long-term conditions.[13]

Abbreviations: A, avoid stroke with anticoagulation; B, better symptom management with rate or rhythm control; C, cardiovascular and comorbidity risk management; OR, odds ratio

We observed that the adherence to specific components of the integrated approach of AF management was relatively high (74% of patients with A-adherent management, 90% with B-adherent management, and 72% with C-adherent management). However, the adherence to all 3 or at least 2 components of ABC holistic approach was still suboptimal. Observed differences in the use of the ABC pathway according to the physician specialty and health center location (ie, better adherence to the ABC management in sites located in capital cities and when treatment was undertaken by a cardiologist) may highlight the system-related barriers to optimal management of AF patients, as well as the knowledge gaps among physicians managing these patients in daily practice. In one study,[23] barriers in the implementation of guideline-recommended AF management specific to physicians and healthcare system in Poland were assessed. The number of significant educational gaps among physicians from Poland and other European countries is low. However, physicians were uncertain about the identification and pathophysiological classification of AF. They also reported suboptimal collaboration with other specialists.

Paroxysmal AF was an independent predictor of decreased A-, B-, and A+B-adherent management. Available data show that patients with paroxysmal AF and conventional stroke risk factors should be anticoagulated. In one study, yearly ischemic stroke rates were 2.1% for paroxysmal AF and 4.2% for permanent AF.[24] Although lower than among patients with permanent AF, annual stroke rates in patients with paroxysmal AF and clinical stroke risk factors are sufficiently high to merit OAC use, hence the pattern of AF should not affect the decision to use OAC.[8] In the Loire Valley Atrial Fibrillation Project,[25] nonpermanent AF was also associated with an increased risk of OAC undertreatment, similarly to our study where paroxysmal AF was associated with decreased adherence to stroke prevention strategy.

Notably, more patients received VKAs than NOACs in both management groups (A+B+C adherent and nonadherent) although NOACs are increasingly recommended as first-line therapy for stroke prevention in AF,[8,26] and the quality of VKA management was poor. Improved A-adherent management included treatment by cardiologist, consistent with another study,[27] and the prevalent use of VKAs might have been related to the local reimbursement policies.

Similar to another study, CAD was a predictor of guideline nonadherence to OAC therapy in our study.[28] According to guidelines, OAC monotherapy is indicated in AF patients with stable CAD without acute coronary syndrome (ACS) and/or percutaneous coronary intervention in the last 12 months.[8] Nevertheless, the use of antiplatelet agents alone was highly prevalent in our study (17% of patients with CHA_2DS_2-VASc score ≥2). Although antiplatelet therapy does not reduce stroke or mortality, it increases the bleeding risk and is not recommended for the prevention of AF-related thromboembolism,[29,30] the use of monotherapy with antiplatelet drugs was still high in some European surveys on AF management.[31-33] The association of CAD with decreased likelihood of A-adherent management in our study may reflect the management of patients with stable CAD and AF using both antiplatelet therapy and OAC, which is not justified owing to increased risk of major bleeding.[34-38]

Overall, the association of OAC use with individual stroke risk assessed using the CHA_2DS_2-VASc score was weak in our study (Supplementary material). Indeed, suboptimal skills in interpreting the CHA_2DS_2-VASc and HAS-BLED scores by neurologists and general practitioners were recently identified in a needs assessment study conducted by the European Society of Cardiology/EHRA, and the uncertainty in interpreting the HAS-BLED score was reported by 32% of participating cardiologists. Moreover, management of complex patients was associated with uncertainty about OAC use.[39] The evident problem regarding stroke prevention in patients with AF in the BALKAN-AF registry was also low-quality anticoagulation (nearly half of the patients on VKA had INR not within therapeutic range).

In our study, 62% of symptomatic patients received rate-control strategy whilst 32% were managed using a rhythm-control strategy. Both strategies are noninferior in relation to mortality, stroke, and hospitalization.[40] However, rhythm-control strategy in short term is linked with improvement in symptoms and functional capacity.[41] β-Blockers were the most commonly used drugs for rate control, whilst amiodarone was most frequently used for rhythm control. Nonpharmacological methods of rhythm control were less commonly used compared with pharmacological

methods. These findings in our study are consistent with other reports.[42,43]

Of note, 72% of patients in our study had their concomitant diseases optimally medicated, and HF, chronic kidney disease, and bleeding events were independently associated with lower likelihood of C-adherent management. Importantly, integrated care facilitates optimal management of hypertension, HF, DM, CAD, and sleep apnea, thus reducing the stroke and cardiovascular risk burden.[1,44] Interestingly, DM was an independent predictor of C- and A+B+C-adherent management. Of note, DM in patients with AF is associated with older age, more comorbidities, higher thromboembolic risk, as well as higher all-cause, cardiovascular, and noncardiovascular mortality.[45] Finally, optimal management of concomitant diseases should be accompanied by lifestyle modifications (obesity reduction, reduction of alcohol consumption, regular exercise) and management of psychological morbidity, and patient values and preferences also need to be considered.[2,46]

There is evidence that education on AF and anticoagulation significantly improved adherence to warfarin.[47] In one study,[48] knowledge on AF and anticoagulation was compared between patients medicated with VKAs and those on NOACs. The knowledge on the abovementioned aspects was similar. However, patients on NOACs had better knowledge concerning safety issues. Moreover, patient's educational level and socioeconomic status were also associated with better adherence to oral anticoagulant therapy in patients with AF.[49] Higher level of education was associated with better patients' awareness of non–vitamin K oral anticoagulants.[50] Unfortunately, the BALKAN-AF registry did not assess the knowledge of the patients on AF and oral anticoagulation, as well as patients' level of education.

Limitations The BALKAN-AF survey has no follow-up data to evaluate outcomes. Data regarding patient / prescriber treatment preferences are lacking. Information on lifestyle modifications is available only in patients with DM and AF, while data on eplerenone use in patients with AF and HF were lacking. Future prospective studies are needed to complement our results.

Conclusions Physicians' adherence to integrated AF management based on the ABC pathway was suboptimal in our study. Addressing the identified clinical or system-related factors associated with A+B+C-nonadherent management using targeted approaches is needed to optimize treatment of patients with AF in the Balkan region.

SUPPLEMENTARY MATERIAL

Supplementary material is available at www.mp.pl/paim.

ARTICLE INFORMATION

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CONTRIBUTION STATEMENT GL and TP conceived the concept of the study. SS, NP, AK, VP, LM, ET, ARD, ZK, G-AD, and TP were involved in data collection. All authors analyzed the data. MK drafted the manuscript. All authors edited and approved the final version of the manuscript.

CONFLICT OF INTEREST G-AD has been consultant for Boehringer Ingelheim, Bayer, Pfizer, and Sanofi. Small speaker fees were received. GYHL has been a consultant for Bayer/Janssen, BMS/Pfizer, Medtronic, Boehringer Ingelheim, Novartis, Verseon, and Daiichi-Sankyo. He has been a speaker for Bayer, BMS/Pfizer, Medtronic, Boehringer Ingelheim, and Daiichi-Sankyo (no fees). TSP has been a consultant for Bayer/Jansen and BMS/Pfizer (no fees). The remaining authors do not report any conflict of interest.

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